

## Elimination of TFA-Mediated Cleavage in Distributed Drug Discovery

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Distributed Drug Discovery (D3) is a multi-disciplinary approach to the discovery of new drugs, which target neglected diseases or conditions common to developing-world countries. As part of a continuing effort to improve D3 methodology, two approaches for eliminating the final step TFA-mediated resin cleavage are proposed for investigation. Cleavage under basic conditions (saponification) and mild acid conditions (dilute HCl/hexafluoroisopropanol or dilute HCl/trifluoroethanol) represent improvements in safety and convenience to the undergraduate student researcher. Previous studies have shown that saponification provides yields comparable to the traditional TFA cleavage but recovery is not as convenient. Further improvements in the saponification workup will be evaluated by analyzing the effectiveness of simple trituration with acetone compared to use of a strong anion-exchange resin or drying reagents to isolate the free acid from the salt. Different trituration procedural modifications have been made and are being tested. Results have shown that in the presence of methanol, esterification will occur when the acid is liberated from the salt using HCl. To counter this problem, the samples are first evaporated to remove methanol and then the pH is adjusted with HCl. It was shown that using acetic acid did not result in pH levels low enough to guarantee complete protonation of the carboxylate. Through the use of a Bill-Board, an apparatus that holds six reaction vessels, several procedural modifications can be carried out simultaneously. Analysis is conducted by liquid chromatography coupled with a mass spectrometer and with nuclear magnetic resonance spectroscopy. Further studies will be carried out to assess the efficiency and practicality of using mild acidic conditions for cleavage using HCl/hexafluoroisopropanol or dilute HCl/trifluoroethanol. Both saponification and mild acid cleavage would represent improvements in safety and convenience to the undergraduate student researcher.

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